



FORM PTO-1449

FIRST SUPPLEMENTAL  
INFORMATION DISCLOSURE STATEMENTATTY. DOCKET NO.  
0609.4460005/JAG/FRCAPPLICATION NO.  
10/052,817APPLICANT  
Tanzi et al.FILING DATE  
January 23, 2002GROUP  
1632

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

9w	AR	31	Non-Provisional United States Patent Application No. 09/925,313, Tanzi et al., filed August 10, 2001
	AS		
	AT		

EXAMINER

Joe Winkler

DATE CONSIDERED

10/14/04

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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
gw	AA1	4,683,195	07/28/1987	Mullis et al.	435	6	02/07/1986
	AB1	5,830,670	11/03/1998	de la Monte et al.	435	7.2	05/30/1995
	AC1	5,948,634	09/07/1999	de la Monte et al.	435	69.1	11/14/1994
	AD1	5,948,888	09/07/1999	de la Monte et al.	530	350	05/30/1995
	AE1	6,071,705	06/06/2000	Wands et al.	435	7.1	06/06/1995
	AF1	6,156,311	12/05/2000	Strickland et al.	424	130.1	07/26/1996
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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
gw	AL1	WO 91/03557	03/21/1991	WIPO			Yes No
	AM1	WO 92/03474	03/05/1992	WIPO			Yes No
	AN1	WO 96/39834	12/19/1996	WIPO			Yes No
	AO1	WO 97/04794	02/13/1997	WIPO			Yes No
	AP1	WO 99/11824	03/11/1999	WIPO			Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

gw	AR	1	"Freely Associating," Nat. Genet. 22:1-2, Nature America, Inc. (May 1999).
	AS	1	Alvarez, V. et al., Association between an $\alpha 2$ Macroglobulin DNA Polymorphism and Late-Onset Alzheimer's Disease," Biochem. Biophys. Res. Commun. 264:48-50, Academic Press, Inc. (October 1999).
	AT	1	Andersen, G.R. et al., "Low Resolution X-Ray Structure of Human Methylamine-treated $\alpha 2$ -Macroglobulin," J. Biol. Chem. 270:25133-25141, American Society for Biochemistry and Molecular Biology, Inc. (1995).

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	AP						Yes No

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94	AR	2	Barrett, A.J. et al., "The Electrophoretically 'Slow' and 'Fast' Forms of the $\alpha$ 2-Macroglobulin Molecule," <i>Biochem. J.</i> 181:401-418, Portland Press, Ltd. (1979).
1	AS	2	Bauer, J. et al., "Interleukin-6 and $\alpha$ 2-macroglobulin indicate an acute-phase state in Alzheimer's disease cortices," <i>FEBS Lett.</i> 285:111-114, Elsevier Science Publisher B.V. (1991).
1	AT	2	Blacker, D. et al., "Correspondence," <i>Nat. Genet.</i> 22:21-22, Nature America, Inc. (May 1999).

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*James W. [Signature]*

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AR	3	Blacker, D. et al., "Alpha-2 macroglobulin is genetically associated with Alzheimer disease," Nat. Genet. 19:357-360, Nature America, Inc. (August 1998).
AS	3	Blennow, K. et al., "No association between the $\alpha$ 2-macroglobulin (A2M) deletion and Alzheimer's disease, and no change in A2M mRNA, protein, or protein expression," J. Neural. Transm. 107:1065-1079, Springer-Verlag (August 2000).
AT	3	Boado, R.J., "Antisense drug delivery through the blood-brain barrier," Adv. Drug Deliv. Rev. 15:73-107, Elsevier Science Publishers B.V. (1995).

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9w	AR	4	Boado, R.J. et al., "Drug delivery of Antisense Molecules to the Brain for Treatment of Alzheimer's Disease and Cerebral AIDS," J. Pharm. Sci. 87:1308-1315, American Pharmaceutical Association (November 1998).
/	AS	4	Borth, W., "α2-Macroglobulin, a multifunctional binding protein with targeting characteristics," FASEB J. 6:3345-3353, FASEB (1992).
/	AT	4	Bowen, M.E. and Gettins, P.G.W., "Bait Region Involvement in the Dimer-Dimer Interface of Human α2-Macroglobulin and in Mediating Gross Conformational Change," J. Biol. Chem. 273:1825-1831, American Society for Biochemistry and Molecular Biology, Inc. (January 1998).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

960	AR	5	Breitaudiere, J-P. et al., "Structure of native $\alpha 2$ -macroglobulin and its transformation to the protease bound form," <i>Proc. Natl. Acad. Sci. USA</i> 85:1437-1441, National Academy Press (1988).
1	AS	5	Businaro, R. et al., "Synthesis and secretion of $\alpha 2$ -macroglobulin by human glioma established cell lines," <i>Exp. Brain Res.</i> 88:213-218, Springer-Verlag (1992).
	AT	5	Cavus, I. et al., "Inhibition of Long-Term Potentiation Development in Rat Hippocampal Slice by $\alpha 2$ -Macroglobulin, an Acute-Phase Protein in the Brain," <i>J. Neurosci. Res.</i> 43:282-288, Wiley-Liss, Inc. (February 1996).

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76	AR	6	Chen, L. et al., "Apolipoprotein E promoter and $\alpha$ 2-Macroglobulin polymorphisms are not genetically associated with Chinese late onset Alzheimer's Disease," <i>Neurosci. Lett.</i> 269:173-177, Elsevier Science Ireland, Ltd. (July 1999).
1	AS	6	Crawford, F. et al., "The alpha-2 macroglobulin gene is not associated with Alzheimer's disease in a case-control sample," <i>Neurosci. Lett.</i> 270:133-136, Elsevier Science Ireland, Ltd. (August 1999).
1	AT	6	Dodel, R.C. et al., " $\alpha$ 2-Macroglobulin and the risk of Alzheimer's disease," <i>Neurology</i> 54:438-442, Lippincott, Williams & Wilkins (January 2000).

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9w	AR	1	Dow, D.J. et al., "α2-macroglobulin polymorphism and Alzheimer disease risk in the UK," Nat. Genet. 22:16-17, Nature America, Inc. (May 1999).
1	AS	1	Du, Y. et al., "α2-Macroglobulin Attenuates β-Amyloid Peptide 1-40 Fibril Formation and Associated Neurotoxicity of Cultured Fetal Rat Cortical Neurons," J. Neurochem. 70:1182-1188, Lippincott-Raven Publishers (March 1998).
1	AT	1	Du, Y. et al., "α2-Macroglobulin as a β-Amyloid Peptide-Binding Plasma Protein," J. Neurochem. 69:299-305, Lippincott-Raven Publishers (July 1997).

EXAMINER

*Joe W. Keller*

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	AN						Yes No
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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

92	AR	8	Fakler, B. et al., "Short Antisense Oligonucleotide-mediated Inhibition Is Strongly Dependent on Oligo Length and Concentration but Almost Independent of Location of the Target Sequence," <i>J. Biol. Chem.</i> 269:16187-16194, American Society for Biochemistry and Molecular Biology, Inc. (1994).
1	AS	8	Feldman, S.R. et al., "Model of $\alpha 2$ -Macroglobulin structure and function," <i>Proc. Natl. Acad. Sci. USA</i> 82:5700-5704, National Academy Press (1985).
1	AT	8	Gauderman, W.J. et al., "Family-Based Association Studies," <i>J. Natl. Cancer Inst. Monogr.</i> 26:31-37, Oxford University Press (December 1999).

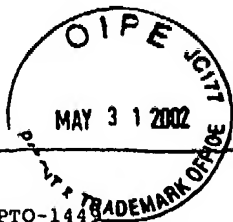
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*Joe L. Fontana*

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

9u	AR	2	Gliemann, J., "Receptors of the Low Density Lipoprotein (LDL) Receptor Family in Man. Multiple Functions of the Large Family Members via Interaction with Complex Ligands," <i>Biol. Chem.</i> 379:951-964, Walter de Gruyter and Company (August/September 1998).
7	AS	2	Hampe, J. et al., "Mapping Genes for Polygenic Disorders: Considerations for Study Design in the Complex Trait of Inflammatory Bowel Disease," <i>Hum. Hered.</i> 50:91-101, S. Karger AG (March-April 2000).
	AT	2	Hardy, J., "Amyloid, the presenilins and Alzheimer's disease," <i>Trends Neurosci.</i> 20:154-159, Elsevier Science, Ltd. (April 1997).

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Joe W. Watake

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9W	AR	10	Hollenbach, E. et al., "Confirmation of an association between a polymorphism in the exon 3 of the low-density lipoprotein receptor-related protein gene and Alzheimer's disease," <i>Neurology</i> 50:1905-1907, Lippincott-Raven Publishers (June 1998).
/	AS	10	Horvath, S. and Laird, N.M., "A Discordant-Sibship Test for Disequilibrium and Linkage: No Need for Parental Data," <i>Am. J. Hum. Genet.</i> 63:1886-1897, University of Chicago Press (December 1998).
/	AT	10	Hu, C-J. et al., "No association of alpha-2 macroglobulin gene five-nucleotide deletion with AD in Taiwan Chinese," <i>Neurology</i> 53:642-643, Lippincott, Williams & Wilkins (August 1999).

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*Joe W. Antack*

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90	AR	11	Hughes, S.R. et al., " $\alpha$ 2-macroglobulin associates with $\beta$ -amyloid peptide and prevents fibril formation," <i>Proc. Natl. Acad. Sci. USA</i> 95:3275-3280, National Academy Press (March 1998).
/	AS	11	Jinnah, H.A. and Friedmann, T., "Gene therapy and the brain," <i>Br. Med. Bull.</i> 51:138-148, Oxford University Press (1995).
/	AT	11	Justus, C.W.E. et al., "Quantification of free $\alpha$ 2-macroglobulin and $\alpha$ 2-macroglobulin-protease complexes by a novel ELISA system based on streptococcal $\alpha$ 2-macroglobulin receptors," <i>J. Immunol. Methods</i> 126:103-108, Elsevier Science Publishers B.V. (1990).

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*Joe W. [Signature]*

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90	AR	12	Kan, C-C. et al., "Nucleotide sequence of cDNA encoding human $\alpha$ 2-macroglobulin and assignment of the chromosomal locus," <i>Proc. Natl. Acad. Sci. USA</i> 82:2282-2286, National Academy Press (1985).
7	AS	12	Kang, D.E. et al., "Genetic association of the low-density lipoprotein receptor-related protein gene (LRP), an apolipoprotein E receptor, with late-onset Alzheimer's disease," <i>Neurology</i> 49:56-61, Lippincott-Raven Publishers (July 1997).
7	AT	12	Kolodziej, S.J. et al., "Three-Dimensional Structure of the Human Plasmin $\alpha$ 2-Macroglobulin Complex," <i>J. Struct. Biol.</i> 123:124-133, Academic Press, Inc. (October 1998).

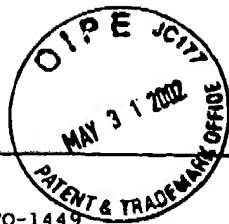
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Joe W. Winters

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	AP						Yes No

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20	AR	13	Korovaitseva, G.I. et al., "Alpha-2 macroglobulin gene in early- and late-onset Alzheimer disease," <i>Neurosci. Lett.</i> 271:129-131, Elsevier Science Ireland, Ltd. (August 1999).
/	AS	13	Koster, M.N. et al., "The $\alpha$ 2-macroglobulin gene in AD. A population-based study and meta-analysis," <i>Neurology</i> 55:678-684, Lipincott, Williams & Wilkins (September 2000).
/	AT	13	Kounnas, M.Z. et al., "LDL Receptor-Related Protein, a Multifunctional ApoE Receptor, Binds Secreted $\beta$ -Amyloid Precursor Protein and Mediates Its Degradation," <i>Cell</i> 82:331-340, Cell Press (1995).

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*Joe W. Lantieri*

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	AN						Yes No
	AO						Yes No
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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1	AS	14	Kounnas, M.Z. et al., "LDL Receptor-Related Protein (LPR) Binds Secreted $\beta$ -Amyloid Precursor Protein and Mediates Its Degradation," <i>Mol. Biol. Cell</i> 6:327A, No. 1901, American Society for Cell Biology (1995).
1	AT	14	Kovacs, D.M. et al., "Alpha-2-Macroglobulin-2 Allele Associated with Alzheimer's Disease: RNA and Protein Products," A Keystone Symposium on Aging: Genetic and Environmental Influences on Life Span. Tamarron, Colorado (February 2-7, 1999).

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90	AR	15	Kovacs, D.M., "α2-Macroglobulin in late-onset Alzheimer's disease," <i>Exper. Gerontol.</i> 35:473-479, Elsevier Science, Inc. (July 2000).
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9w	AR	16	Lake, S.L. et al., "Family-Based Tests of Association in the Presence of Linkage," <i>Am. J. Hum. Genet.</i> 67:1515-1525, University of Chicago Press (December 2000).
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76	AR	17	Lopes, M.B.S. et al., "Expression of $\alpha 2$ -macroglobulin receptor/low density lipoprotein receptor-related protein is increased in reactive and neoplastic glial cells," <i>FEBS Lett.</i> 338:301-305, Elsevier Science Publisher B.V. (1994).
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90	AR	18	Marynen, P. et al., "A genetic polymorphism in a functional domain of human pregnancy zone protein: the bait region," <i>FEBS Lett.</i> 262:349-352, Elsevier Science Publishers B.V. (1990).
1	AS	18	Matthijs, G. and Marynen, P., "A deletion polymorphism in the human alpha-2-macroglobulin (A2M) gene," <i>Nucleic Acids Res.</i> 19:5102, Oxford University Press (1991).
1	AT	18	Misra, U.K. and Pizzo, S.V., "Binding of Receptor-recognized Forms of $\alpha$ 2-Macroglobulin to the $\alpha$ 2-Macroglobulin Signaling Receptor Activates Phosphatidylinositol 3-Kinase," <i>J. Biol. Chem.</i> 273:13399-13402, American Society for Biochemistry and Molecular Biology, Inc. (May 1998).

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9w	AR	12	Mori, T. et al., "α2-Macroglobulin is an astroglia-derived neurite-promoting factor for cultured neurons from rat central nervous system," <i>Brain Res.</i> 527:55-61, Elsevier Science Publisher B.V. (1990).
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*Joe Wotasek*

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

90	AR	20	Nielsen, K.L. et al., "Identification of Residues in $\alpha$ -Macroglobulins Important for Binding to the $\alpha$ 2-Macroglobulin Receptor/Low Density Lipoprotein Receptor-related Protein," J. Biol. Chem. 271:12909-12912, American Society for Biochemistry and Molecular Biology, Inc. (May 1996).
1	AS	20	Poller, W. et al., "Cloning of the human $\alpha$ 2-macroglobulin gene and detection of mutations in two functional domains: the bait region and the thiolester site," Hum. Genet. 88:313-319, Springer-Verlag (1992).
1	AT	20	Poller, W. et al., "Sequence polymorphism in the human alpha-2-macroglobulin (A2M) gene," Nucleic Acids Res. 19:198, Oxford University Press (1991).

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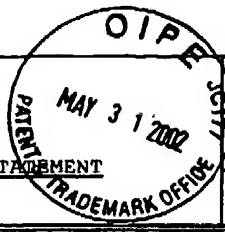
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	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

9W	AR	21	Qiu, W.Q. et al., "Degradation of Amyloid $\beta$ -Protein by a Serine Protease- $\alpha$ 2-Macroglobulin Complex," J. Biol. Chem. 271:8443-8451, American Society for Biochemistry and Molecular Cell Biology, Inc. (April 1996).				
1	AS	21	Rebeck, G.W. et al., "Multiple, Diverse Senile Plaque-associated Proteins Are Ligands of an Apolipoprotein E Receptor, the $\alpha$ 2-Macroglobulin Receptor/Low Density-Lipoprotein Receptor-related Protein," Ann. Neurol. 37:211-217, Lippincott, Williams & Wilkins (1995).				
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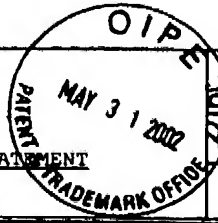
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76	AR	22	Rogaeva, E.A. et al., "An $\alpha$ 2-macroglobulin insertion-deletion polymorphism in Alzheimer disease," Nat. Genet. 22:19-21, Nature America, Inc. (May 1999).				
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1	AT	22	Rudrasingham, V. et al., " $\alpha$ 2-macroglobulin gene and Alzheimer disease," Nat. Genet. 22:17-19, Nature America, Inc. (May 1999).				

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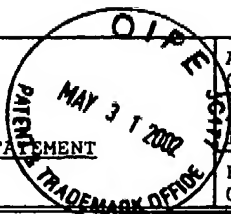
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90	AR	23	Selkoe, D.J. et al., "Cell biology of the amyloid $\beta$ -protein precursor and the mechanism of Alzheimer's disease," <i>Annu. Rev. Cell Biol.</i> 10:373-403 (1994).
7	AS	23	Shibata, N. et al., "Genetic association between alpha-2 macroglobulin and Japanese sporadic Alzheimer's disease," <i>Neurosci. Lett.</i> 271:132-134, Elsevier Science Ireland, Ltd. (August 1999).
	AT	23	Singleton, A.B. et al., " $\alpha$ 2-Macroglobulin polymorphisms in Alzheimer's disease and dementia with Lewy bodies," <i>NeuroReport</i> 10:1507-1510, Lippincott, Williams & Wilkens (May 1999).

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96	AR	24	Sodeyama, N. et al., "α2-Macroglobulin polymorphism is not associated with AD or AD-type neuropathology in the Japanese," <i>Neurology</i> 54:443-446, Lippincott, Williams & Wilkins (January 2000).				
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	AT	24	Soto, C. et al., "β-Sheet breaker peptides inhibit fibrillogenesis in a rat brain model of amyloidosis: Implications for Alzheimer's therapy," <i>Nat. Med.</i> 4:822-826, Nature America, Inc. (July 1998).				

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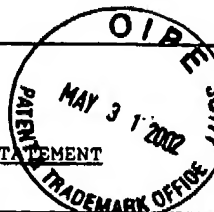
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70	AR	25	Sottrup-Jensen, L. et al., "Primary Structure of Human $\alpha$ 2-Macroglobulin," J. Biol. Chem. 259:8318-8327, American Society of Biological Chemists, Inc. (1984).
1	AS	25	Stratagene, 1988 Catalog, "Gene Characterization Kits," La Jolla, CA (February 1997).
1	AT	25	Strauss, S. et al., "Detection of Interleukin-6 and $\alpha$ 2-Macroglobulin Immunoreactivity in Cortex and Hippocampus of Alzheimer's Disease Patients," Lab. Invest. 66:223-230, Lippincott, Williams & Wilkins (1992).

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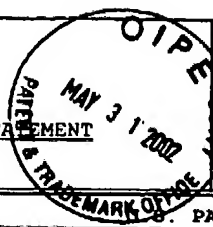
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	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

76	AR	26	Strickland, D.K. et al., "Sequence Identity between the $\alpha$ 2-Macroglobulin Receptor and Low Density Lipoprotein Receptor-related Protein Suggests That This Molecule Is a Multifunctional Receptor," <i>J. Biol. Chem.</i> 265:17401-17404, American Society for Biochemistry and Molecular Biology, Inc. (1990).
1	AS	26	Strickland, D.K. et al., "Primary Structure of $\alpha$ 2-Macroglobulin Receptor-associated Protein. Human Homologue of a Heymann Nephritis Antigen," <i>J. Biol. Chem.</i> 266:13364-13369, American Society for Biochemistry and Molecular Biology, Inc. (1991).
1	AT	26	Tanzi, R.E. et al., "Amyloid $\beta$ protein Gene: cDNA, mRNA Distribution, and Genetic Linkage Near the Alzheimer Locus," <i>Science</i> 235:880-884, American Association for the Advancement of Science (1987).

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## INFORMATION DISCLOSURE STATEMENT

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## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA						
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

96	AR	27	Tanzi, R.E., "A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorders," <i>J. Clin. Invest.</i> 104:1175-1179, American Society for Clinical Investigation (November 1999).				
1	AS	27	Tirode, F. et al., "A Conditionally Expressed Third Partner Stabilizes or Prevents the Formation of a Transcriptional Activator in a Three-hybrid System," <i>J. Biol. Chem.</i> 272:22995-22999, American Society for Biochemistry and Molecular Biology, Inc. (September 1997).				
	AT	27	Tooyama, I. et al., "Immunohistochemical Study of $\alpha 2$ Macroglobulin Receptor in Alzheimer and Control Postmortem Human Brain," <i>Mol. Chem. Neuropathol.</i> 18:153-160, Humana Press, Inc. (1993).				

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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

gw	AR	28	Van Gool, D. et al., "α2-Macroglobulin Expression in Neuritic-Type Plaques in Patients with Alzheimer's Disease," <i>Neurobiol. Aging</i> 14:233-237, Pergamon Press, Ltd. (1993).
	AS	28	Van Leuven, F. et al., "The Receptor-binding Domain of Human α2-Macroglobulin. Isolation after Limited Proteolysis with a Bacterial Proteinase," <i>J. Biol. Chem.</i> 261:11369-11373, American Society of Biological Chemists, Inc. (1986).
	AT	28	Verpillat, P. et al., "α2-Macroglobulin Gene and Alzheimer's Disease: Confirmation of Association by Haplotypes Analyses," <i>Ann. Neurol.</i> 48:400-402, Lippincott, Williams & Wilkins (September 2000).

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## PATENT DOCUMENTS

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

96	AR	29	Wavrant-DeVrièze, F. et al., "Association between the low density lipoprotein receptor-related protein (LRP) and Alzheimer's disease," <i>Neurosci. Lett.</i> 227:68-70, Elsevier Science Ireland, Ltd. (May 1997).				
	AS	29	Wavrant-DeVrièze, F. et al., "No association between the alpha-2 macroglobulin 11000V polymorphism and Alzheimer's disease," <i>Neurosci. Lett.</i> 262:137-139, Elsevier Science Ireland, Ltd. (March 1999).				
	AT	29	Zhang, Z. et al., "Inhibition of $\alpha$ 2-macroglobulin/proteinase-mediated degradation of amyloid $\beta$ peptide by apolipoprotein E and $\alpha$ 1-antichymotrypsin," <i>Int. J. Exp. Clin. Invest.</i> 3:156-161, Parthenon Publishing (September 1996).				

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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL2						Yes No
	AM2						Yes No
	AN2						Yes No
	AO2						Yes No
	AP2						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

gw	AR	30	Zill, P. et al., "Polymorphisms in the $\alpha$ 2-macroglobulin gene in psychogeriatric patients," <i>Neurosci. Lett.</i> 294:69-72, Elsevier Science Ireland, Ltd. (November 2000).
	AS	30	International Search Report for International Application No. PCT/US00/02412, mailed July 6, 2000.
	AT	30	Copy of co-pending U.S. Application No. 60/337,434, Becker et al., filed November 9, 2001.

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